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**REMARKS**

**Status of the Claims**

Claims 34-44 and 58-67 are pending herein.

Support for the claim amendments and the new claims can be found, for example, in paragraphs [0095] to [0098] of the specification. No new matter is added.

**Claim Rejection under 35 U.S.C. §112, first paragraph**

Claims 34-37, 39, 42-44 and 58-61 are rejected under 35 U.S.C. §112, first paragraph, because the specification allegedly does not provide enablement for using *all* detergents in the preparation of microparticles. Applicant respectfully traverses this rejection and its supporting remarks.

For example, citing *Wands*, the Examiner argues that the *working examples* (see Examples 1-5) are limited to microparticle compositions that are (a) washed after microparticle formation and (b) are limited to PVA and CTAB. Thus, the *guidance* provided by applicant is limited to the preparation of microparticles with a washing step where CTAB and PVA are the detergents. Consequently, a person of ordinary skill in the art would have to perform an undue amount of experimentation to determine other suitable detergents for use in applicant's invention.

The Examiner further argues that because Example 6, the only working example where microparticles are specifically disclosed as not being washed, is limited to CTAB, a person of ordinary skill in the art would have to perform a undue amount of experimentation to determine other suitable cationic detergents for use in applicant's invention.

As presently amended, the claims of the present application are directed to methods in which (1) microparticles are formed by forming an emulsion comprising a polymer, an organic solvent, a detergent and water, followed by removal of the organic solvent from the emulsion and either (2a) subjecting the microparticles to a filtration step such that about 10-90% of the total detergent in the microparticle composition is bound to the microparticles and the remainder is unbound or (2b) not subjecting the microparticles to a washing step, while selecting the ratio of the detergent to the polymer ratio such that

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about 10-90% of the total detergent in the microparticle composition is bound to the microparticles and the remainder is unbound.

One of ordinary skill in the art would clearly have sufficient guidance to create microparticle compositions having the claimed percentages of bound and unbound detergent using a variety of detergents, without subjecting the compositions to a washing step. This could be achieved without undue experimentation, for example, by selecting a suitable detergent-to-polymer ratio as taught in paragraph [0098].

One of ordinary skill in the art would also clearly have sufficient guidance to create microparticle compositions having the claimed percentages of bound and unbound detergent using a variety of detergents, by subjecting the compositions to a filtration step. This could be achieved without undue experimentation, for example, by selecting an appropriate amount of water (otherwise known as the diafiltration solution) for use within the cross-flow apparatus. In this regard, see, e.g., the attached introductory materials on cross-flow filtration, also known as Tangential Flow Filtration (TFF), in which diafiltration is described for use in separating smaller species (in the present invention, detergent molecules) from larger species (in the present invention, microparticles). An increase in diafiltration volume (DV) reduces the concentration of the smaller species in the composition, and vice versa. This is routine knowledge in the cross-flow filtration art.

In this regard, it is noted from MPEP 2164.06 that the amount of experimentation can be extensive:

..."[A]n extended period of experimentation may not be undue if the skilled artisan is given sufficient direction or guidance." *In re Colianni*, 561 F.2d 220, 224, 195 USPQ 150, 153 (CCPA 1977). "The test is not merely quantitative, since a considerable amount of experimentation is permissible, if it is merely routine, or if the specification in question provides a reasonable amount of guidance with respect to the direction in which the experimentation should proceed." *In re Wands*, 858 F.2d 731, 737, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988) (citing *In re Angstadt*, 537 F.2d 489, 502-04, 190 USPQ 214, 217-19 (CCPA 1976))....

It is further noted from MPEP 2164.04 that the examiner has the initial burden to establish a reasonable basis to question the enablement provided for the claimed invention.

Reconsideration and withdrawal of the outstanding rejection under 35 U.S.C. §112, first paragraph are therefore respectfully requested.

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**Claim Rejection under 35 U.S.C. §112, second paragraph**

Claims 34-44 and 58-61 are rejected under 35 U.S.C. §112, second paragraph. Applicant respectfully traverses this rejection and its supporting remarks.

The Office argues (a) that the disclosure stipulates that the amount of detergent must be low to avoid a washing step that would remove excess detergent, and (b) because certain claims do not indicate the limit of detergent amount at which there would be a washing step, the scope of claims is not commensurate with what is disclosed to be essential to avoid filtration or washing.

In particular, the Office points to the portion of paragraph [0025] in which states as follows: "In a specific embodiment, the cationic detergent is CTAB, the polymer is poly(D,L-lactide-co-glycolide), the cationic detergent is provided in the emulsion at a weight to weight detergent to polymer ratio of from about 0.002:1 to about 0.04:1, and the microparticles are not subjected to a step to remove excess CTAB from the composition."

The preceding sentence, however, has been taken out of context as it immediately follows the following sentence: "At these lower levels [i.e., at a weight to weight detergent to polymer ratio of from about 0.001:1 to about 0.05:1], there is typically no need for a filtration or washing step to remove excess detergent." Thus the portion of paragraph [0025] reference in the Office Action is simply a *specific embodiment* exemplifying *typical* detergent to polymer ratios in which a filtration or washing step is employed to remove excess detergent. It does not establish an absolute limit on the detergent amount at which there would be a washing or filtration step.

Moreover, this rejection is now believed to be moot in view of the above amendments to the claims. Specifically, only claim 39 presently requires the absence of a washing step. This claim also sets forth a weight to weight detergent to polymer ratio of from about 0.001:1 to about 0.05:1, thus establishing upper and lower limits for which there would not be a washing step. Thus, this claim is consistent even with the Office's interpretation of the teachings of paragraph [0025].

Reconsideration and withdrawal of the rejection of the claims under 35 U.S.C. §112, second paragraph are requested.

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**Claim Rejection under 35 U.S.C. 103-Levy in view of Paliard**

Claims 34-44 and 58-61 are rejected under 35 U.S.C. 103(a) as unpatentable over US 6,395,253 to Levy et al. (Levy) in view of US 6,562,346 to Paliard et al. (Paliard).

Applicant respectfully traverses this rejection and its supporting remarks.

The claimed invention relates to new methods for the production of microparticle compositions. As explained in the present application at [0011] onwards:

*The present inventors have found that adsorption of macromolecules to microparticles can be improved by ensuring that detergent is made available for forming a complex with the macromolecules at the time of adsorption. This availability can be accomplished, for example, by separately providing a quantity of detergent at the time of macromolecule adsorption or by ensuring that the process for producing the microparticles results in a product containing a substantial amount of unbound detergent.*

Thus, the application teaches two different ways of "ensuring that detergent is made available for forming a complex with the macromolecules at the time of adsorption".

In response to the prior Office Action mailed August 6, 2004, it was noted that, upon reviewing Levy, one of ordinary skill in the art would have followed Levy's procedures, as set forth in the Examples, to produce microspheres. In particular, Levy teaches a method of producing microspheres comprising forming a W/O/W emulsion, evaporating the organic solvent from the W/O/W emulsion, recovering microspheres by ultracentrifugation, and washing recovered microspheres multiple times. See, e.g., the Examples of Levy. Nowhere in Levy is it suggested that one should separately provide a quantity of detergent at the time of macromolecule adsorption, or ensure that the process for producing the microparticles results in a product containing a substantial amount of unbound detergent to improve macromolecule adsorption to the microparticles, as disclosed by the present application.

The Examiner argues that while the Examples of Levy disclose a washing step, Section 4.2 does not. Respectfully, Section 4.2 discloses a basic process for making microspheres containing bioactive agents. A basic process for making microspheres with encapsulated bioactive agents would not have led one of ordinary skill in the art to reasonably conclude that macromolecule adsorption to microparticles can be improved by "ensuring that detergent is made available for forming a complex with the

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macromolecules at the time of adsorption". Thus, Levy does not reasonably suggest in Section 4.2 that one ensure that detergent be made available for forming a complex with the macromolecules at the time of adsorption. Levy also does not reasonably suggest that by doing so, one would obtain a microparticle composition that benefits from improved macromolecule adsorption properties.

Moreover, it is respectfully submitted that one of ordinary skill in the art would not read Section 4.2 in a manner that is decoupled from the Examples. See MPEP 2141.02.VI: A prior art reference must be considered in its entirety, i.e., as a whole, including portions that would lead away from the claimed invention. *W.L. Gore & Associates, Inc. v. Garlock, Inc.*, 721 F.2d 1540, 220 USPQ 303 (Fed. Cir. 1983), *cert. denied*, 469 U.S. 851 (1984).

The Office also argues the following:

Regarding the argument that 10-90% of the total detergent in the microparticle composition is bound to the microparticle[s], with the remaining 10-90% unbound, it is respectfully noted that the claims do not recite the starting amount of the detergent to effect the amount bound, and the amount of the bound and the unbound are the same as the applicants state. Since there is no specific recitation of the starting amount of the detergent, ... the same bound/unbound detergent would be expected for the process of Levy."

Applicant respectfully disagrees. The fact that the applicant's claims do not recite the starting amount of the detergent is irrelevant; what is relevant is the amount of the bound and unbound detergent remaining after the processes are conducted as claimed. The claims encompass the two ways of "ensuring that detergent is made available for forming a complex with the macromolecules at the time of adsorption" disclosed in the application at [0011]. As a result, adsorption of macromolecules to the microparticles is improved (see the application at [0011]). In contrast, Levy teaches washing and centrifugation which would not yield the claimed amounts of bound and unbound detergent.

Furthermore, as discussed above, in Levy, the biologically active macromolecule is incorporated into the microspheres at the time of microsphere formation. In pending claims 43, 44 and 58-61, on the other hand, the microparticle composition is incubated with a biologically active macromolecule after microparticle formation. By ensuring a process in which 10-90% of the total detergent in the microparticle composition remains

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unbound to the microparticles, detergent is made available for forming a complex with the macromolecules at the time of adsorption. See, e.g., paragraph [0011] of the present specification.

In addition to ensuring that detergent is made available for complex formation with macromolecules, the processes of the present invention are advantageous relative to those of Levy, *inter alia*, because they do not require a centrifugation step. This is extremely unwieldy from a manufacturing standpoint. By avoiding the need for a centrifugation step, the manufacturing process is greatly simplified, allowing for efficient scale up and for continuous manufacturing processing, as desired.

Paliard, which cited for its disclosure of CTAB as a detergent, does not make up for the above noted deficiencies in Levy. For example, as elsewhere in the art at the time of the invention, washing is taught in Paliard in Example 5 (see col. 23, lines 53-55).

"The totality of the prior art must be considered, and proceeding contrary to accepted wisdom in the art is evidence of nonobviousness." MPEP 2145.X.D.3. Citing *In re Hedges*, 783 F.2d 1038, 228 USPQ 685 (Fed. Cir. 1986).

For at least the above reasons, it is respectfully submitted that the cited references do not support a *prima facie* case of obviousness against claims 34-44 and 58-61.

Reconsideration and withdrawal of the rejection of the claims under U.S.C. 103(a) as unpatentable over O'Hagan in view of Paliard are respectfully requested.

**Claim Rejection under 35 U.S.C. 103-O'Hagan**

Claims 34, 35, 36, 42 and 43 are rejected under 35 U.S.C. 103(a) as unpatentable over US 6,086,901 to O'Hagan et al. (O'Hagan). Applicant respectfully traverses this rejection and its supporting remarks.

In this regard, the Office argument appears to be as follows: O'Hagan discloses in Example 1 the process of preparing an emulsion that comprises PLG, solvent and detergent. The cross-flow filtration process of Example 5 uses 4 liters of deionized water to remove excess CTAB, and thus appears to approximate a washing process. Consequently, claims 34, 35, 36, 42 and 43, which read on the cross-flow filtration processes, are not patentably distinguishable from the process of O'Hagan, in which particles are washed.

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In Example 1, O'Hagan teaches a method for preparing antigen-entrapped microparticles. In addition, O'Hagan does not appear to teach or suggest the use of filtration techniques a claimed, but rather describes centrifugation, as do Levy and Paliard above. See, for instance, Example 1, col. 14, lines 62-63 (washed three times using centrifugation) and Example 3, col. 16, lines 3-4 (also washed three times using centrifugation).

O'Hagan also does not teach or suggest that one should separately provide a quantity of detergent at the time of macromolecule adsorption, or ensure that the process for producing the microparticles results in a product containing a substantial amount of unbound detergent to improve macromolecule adsorption to the microparticles, as disclosed by the present application. In particular, O'Hagan does not teach a process in which about 10-90% of the total detergent in the microparticle composition is bound to the microparticles, with the remainder (i.e., 10-90%) unbound.

As with Levy above, the Office argues that since there is no specific recitation of the starting amount of the detergent in applicant's claims, the same bound/unbound detergent would be expected for the process of O'Hagan.

Applicant respectfully disagrees. As noted in paragraph [0011] of the specification, techniques in which microparticles are washed multiple times with water, such as the process of O'Hagan, remove essentially all unbound detergent, resulting in a final product in which greater than 99% of the remaining detergent is bound to the particles.

For at least these reasons, it is believed that claims 34, 35, 36, 42 and 43 are patentable over O'Hagan. Reconsideration and withdrawal of the rejection of these claims over O'Hagan are respectfully requested.

### CONCLUSION

Applicants submit that the claims of the present invention are in condition for allowance, early notification of which is earnestly solicited. Should the Examiner be of the view that an interview would expedite consideration of this Amendment or of the application at large, request is made that the Examiner telephone the Applicant's attorney at (703) 433-0510 to resolve any outstanding issues.

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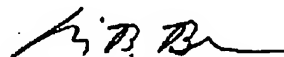
**FEES**

The Office is authorized to charge any additional fees required to deposit account number 50-1047.

**CORRESPONDENCE**

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Respectfully submitted,



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